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Please find below and/or attached an Office communication concerning this application or proceeding.

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/885,287
Filing Date: June 21, 2001
Appellant(s): SEWING ET AL.

Jennifer Branigan
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8-11-08 appealing from the Office action mailed 2-8-08.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5167961	LUSSI et al.	12-1992
4780450	SAUK et al.	10-1988

5279831	CONSTANTZ et al.	01-1984
5543441	RHEE et al.	8-1996
5573771	GIESTLICH et al.	11-1996
6300315	LIU	10-2001
6524718	WORCH et al.	2-2003
5205921	SHIRKANZADEH	4-1993
JP11-047259	SULZER CALCITEK	02-1999

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

1. Claims 1, 4, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in further view of Lussi et al (5,167,961) as evidenced by US 5,543,441.

JP teaches a prosthetic implant coated with hydroxyapatite (HA). The implants provide an implant that is close to osseous tissue and such implants fully "unite with existing osseous tissue and will promote growth of the new bone". [002]. The coating contains highly crystalline hydroxyapatite and low content of amorphous calcium phosphate. See abstract. The examples teach coating a titanium-alloy implant. The

coating also has a low content of tricalcium phosphate and doped with carbonate. See examples and [0080].

JP does not teach the particle size of HA or collagen.

Constantz teaches a hydroxyapatite prosthesis coating which allows for ingrowth of natural bone. See abstract. The method involves combining a soluble source of calcium with a soluble source of phosphate under conditions of controlled nucleation and modulated crystal growth to form a multilayered hydroxyapatite coating on a substrate. Constantz teaches the use of other ions and components to modify the HA composition such as using fluoride, carbonate, hydrogen, etc, which influence the dissolution behavior of the coating. See column 2, lines 50-60. Constantz teaches the coating composition may further comprise collagen and growth factors to enhance bony ingrowth. See column 6, lines 1-10. The composition is coated on a steel or titanium. See column 6, lines 14-20. The crystals have a diameter of 0.01microns (10nm) to 20 microns (20000nm) (see column 2, line 60) and a length of 0.01 microns (10nm) to about 10 microns (10000nm) (see column 3, line 40). Constantz teaches a first layer of the coating with a thickness of 0.01microns (10nm) to 20 microns (20000nm). See column 3, lines 39-41.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatite-like crystallites with a particular degree of crystallinity, habit and size (irregular plate like morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-

5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodeled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4, lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodeling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodeling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20.

Firstly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of JP and Constantz et al and further

add collagen to the hydroxyapatite coating. One would have been motivated to do so since Constantz teaches a HA coating composition that may further comprise collagen and growth factors to enhance bone growth. A skilled artisan would have reasonably expected similar results since both references are in the same filed of endeavor, i.e. implants coated with hydroxyapatite compositions. With regard to claim 4, a skilled artisan would have been motivated to add other ions such as fluoride or carbonate to manipulate the resorption rate of the coating. Further, Constantz teaches various particles sizes of HA that are suitable for HA coating compositions.

Secondly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of JP and Lussi et al and specifically utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster. A skilled artisan would have reasonably expected similar results since JP teaches the purpose of the hydroxyapatite coating on implants since to provide a surface for bone ingrowth and to mimic natural bone.

Regarding the product-by-process limitations, MPEP section 2113 states "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the

same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985). With regard to the layers, collagen in combination with mineral components implicitly tends to separate into phases or layers. Note US 5,543,441, column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's position.

2. **Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view Sauk et al (4,780,450).**

The teachings of JP, Constantz, and Lussi, have been set forth above.

The references do not specify the instant collagen combination, i.e. type I and type III.

Sauk et al teach a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). Sauk teaches the collagen provides a structural matrix preventing migration of the calcium particles and the calcium phosphate particles also interact with the collagen to improve the physical properties of the collagen matrix by reducing its compressibility and increasing its mechanical strength. Sauk teaches not only does the combination provide a scaffold for new bone ingrowth but it mimics natural bone. A mixture of type I and type III collagen is taught (example 1). Sauk et al teach in column 2, line 60 to column 3, line 5, "the

composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of above references and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

3. Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Geistlich et al (5,573,771).

The teachings of JP, Constantz, and Lussi, have been set forth above.

The references do not teach the use of gelatin.

Geistlich teaches a bone mineral product that comprises collagen (Type I or Type I-III), gelatin, and calcium phosphate components. The reference teaches gelatin provides strength and freedom from antigenicity. See column 2, lines 20-30. Further, the reference teaches the use of active agents such as growth factors, antibiotics, etc to allow the bone to be used as a drug carrier. See column 3, lines 20-65.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references and further add gelatin to JP's coating composition. One would have been motivated to do so since Geistlich

teaches gelatin not only adds strength to bone mineral products but it also reduces an adverse immune response.

4. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Liu (6,300,315).

The teachings of JP, Constantz, and Lussi, have been set forth above.

The references do not teach the use of additional calcium phosphates as claimed in claim 3.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at

lest a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the above references and Liu and further add calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including tricalcium phosphate, hydroxyapatite, amorphous calcium phosphate, octacalcium phosphate to provide a strong and flexible membrane. Further, JP teaches the coating has a small weight percent of tricalcium phosphate; thus if a skilled artisan desired to utilize octacalcium phosphate in place of tricalcium phosphate, a skilled artisan would have been motivated to substitute accordingly in view of Liu's teaching that the mineral phase may be made of a mixture of calcium phosphates.

5. Claims 1, 3-5, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441.

Worch et al disclose a metallic substrate (titanium) having a polyphase oxide coating. The polyphase oxide coating is produced by bringing the metallic substrate into contact with an organic and/or inorganic component to be integrated into the polyphase

oxide coating such that the inorganic and/or organic phases are present at or in the direct vicinity of the substrate surface and by simultaneously or subsequently anodically polarizing the substrate material in an electrolytic solution. See abstract. The process of coating the implant yields a two-layer oxide coating, where the outer layer is the inorganic and/or the organic phase. See column 2, lines 32-45. The inorganic component is calcium phosphate and the organic component is Type I collagen. See column 2, lines 46-60. Claim 1 envisages a combination of an organic phase and inorganic phase and claim 4 envisages calcium phosphate as the inorganic phase. Example 1 discloses a coating thickness of 250 nm (.250 micrometers) on the metallic implant. Worch discloses a process wherein the metallic implant is immersed in a collagen solution at the instant pH and temperature and then coated again with a phosphate solution. Note that the use of calcium ions in this solution is clearly envisaged as noted in column 2, lines 46-60 and claim 4.

Although Worch teaches the use of calcium phosphates as the inorganic phase, Worch does not teach specify the form of calcium phosphate or the size of the calcium phosphate. Also Worch does not teach the incorporation of components as recited in claim 4 (doping agents) or 8 (medicaments).

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium

phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at least a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatite like crystallites with a particular degree of crystallinity, habit and size (irregular plate like morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodeled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new

bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4, lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted; it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodeling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodeling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20. .

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Worch and Liu and utilize calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly clamed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen. Further, Worch teaches the combination of calcium

phosphate phases and collagen wherein it is clear that Worch contemplates utilizing more than one form of calcium phosphate. Further, on column 1, lines 45-55, Worch states the deficiency of the prior art is that it only utilizes resorbable calcium phosphate and not hydroxyapatite and thus “the complete character of the implant is lost”. Thus, one would have expected success with the instant combination since Worch implicitly teaches a combination of hydroxyapatite and resorbable calcium phosphate (not crystallized calcium phosphate). With regard to the instantly claimed doping agents, it would have been obvious to dope Worch’s mineralized collagen since Liu teaches the adding minor portions of fluoride or carbonate to the mineralized collagen to provide certain desired properties and to resemble or simulate biological apatite. With regard to the instantly claimed drugs, it would have been obvious to add certain drugs depending on the desired effect of the implant as taught by Liu.

Secondly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Worch, Liu, and Lussi et al and utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster.

Regarding the product-by-process limitations, MPEP section 2113 states “even though product by process claims are limited by and defined by the process,

determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to the layers, it is the examiner's position that collagen in combination with mineral components implicitly tends to separate into phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's position.

6. Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Sauk et al (4,780,450).

The teachings of Worch, Liu, and Lussi, have been set forth above.

The references do not specify the instant collagen combination, i.e. type I and type III. Sauk et al disclose a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). A mixture of type I and type III collagen is taught (example 1). Sauk et al disclose in column 2, line 60 to column 3, line 5, "the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic. These compositions are intended to facilitate matrix-mediated mineralization, whereby the collagen defines a

structural matrix and the salt regulates and directs mineral deposition in terms of its location, crystallinity and association with the calcium phosphate ceramic particles.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of Worch, Liu, Lussi, and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

7. Claims 1, 3-4, 8, 10, 12--16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441.

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium

phosphate. The calcium phosphate is selected from either tricalcium phosphate and hydroxyapatite is taught. See claims and examples. The micropores in the calcium phosphate compound coating also encourages better adhesion of collagen. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

The reference does not teach the combination of amorphous calcium phosphate and hydroxyapatite (HA) or the instant particle size of HA.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite (HA), and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at least a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatite-like crystallites with a particular degree of crystallinity, habit and size (irregular plate-like morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodeled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4, lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodelling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have

adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20. .

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Shirkanzadeh and Liu and utilize the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly clamed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen.

Secondly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Shirkanzadeh, Liu, and Lussi et al and utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. It is noted that although Shirkanzadeh teaches the final coating comprises a network of crystals with a size of 2-5 microns, Shirkanzadeh does not teach away from using other particle sizes. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster.

Regarding the product-by-process limitations, MPEP section 2113 states “even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985). It is noted that
With regard to layers, it is noted that collagen in combination with mineral components implicitly tends to separate into phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner’s argument.

8. Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in view of Sauk et al (4,780,450).

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate,

may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium phosphate. The particle range of the calcium phosphate is 2-5 microns. See example 2. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

The reference does not specify the instant collagen combination, i.e. type I and type III.

Sauk et al disclose a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). A mixture of type I and type III collagen is taught (example 1). Sauk et al disclose in column 2, line 60 to column 3, line 5, “the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic. These compositions are intended to facilitate matrix-mediated mineralization, whereby the collagen defines a structural matrix and the salt regulates and directs mineral deposition in terms of its location, crystallinity and association with the calcium phosphate ceramic particles.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of Shirkanzadeh et al and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

9. Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Geistlich et al (5,573,771).

The teachings of Shirkanzadeh, Lui, and Lussi, have been set forth above.

The references do not teach the use of gelatin.

Geistlich teaches a bone mineral product that comprises collagen (Type I or Type I-III), gelatin, and calcium phosphate components. The reference teaches gelatin provides strength and freedom from antigenicity. See column 2, lines 20-30. Further, the reference teaches the use of active agents such as growth factors, antibiotics, etc to allow the bone to be used as a drug carrier. See column 3, lines 20-65.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references and further add gelatin to the coating composition. One would have been motivated to do so since Geistlich teaches gelatin not only adds strength to bone mineral products but it also reduces an adverse immune response.

10. Claims 1, 3-6, 8, 10, 12-16, 18-19, 23-25, 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Constantz et al (5,279,831) in view of Liu (6,300,315) optionally in further view of Lussi et al (5,167,961) and as evidenced by US 5,543,441.

Constantz teaches a hydroxyapatite prosthesis coating which allows for ingrowth of natural bone. See abstract. The method involves combining a soluble source of calcium with a soluble source of phosphate under conditions of controlled nucleation and modulated crystal growth to form a multilayered hydroxyapatite coating on a substrate. Constantz teaches the use of other ions and components to modify the HA composition such as using fluoride, carbonate, hydrogen, etc, which influence the dissolution behavior of the coating. see column 2, lines 50-60. Constantz teaches the coating composition may further comprises <u>collagen</u> and growth factors to enhance bony ingrowth. See column 6, lines 1-10. The composition is coated on a steel or titanium. See column 6, lines 14-20. The crystals have a diameter of 0.01microns (10nm) to 20 microns (20000nm) (see column 2, line 60) and a length of 0.01 microns (10nm) to about 10 microns (10000nm) (see column 3, line 40). Constantz teaches a first layer of the coating with a thickness of 0.01microns (10nm) to 20 microns (20000nm). See column 3, lines 39-41.

Constantz does not teach the use of amorphous calcium phosphate or additional calcium phosphates as claimed in claim 3.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. Liu teaches the mineralized collagen membrane is thin, strong, and flexible. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate mineral component is selected from tri-calcium phosphate, octa-

calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. The mineralized collagen provides mechanical properties superior co art of interest to support examiner's argument compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at lest a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Constantz and Liu and utilize the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly clamed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of JP and Lussi et al and specifically utilize the instant particle size. One would have been motivated to do so since Lussi

teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster. A skilled artisan would have reasonably expected similar results since JP teaches the purpose of the hydroxyapatite coating on implants since to provide a surface for bone ingrowth and to mimic natural bone.

Regarding the product-by-process limitations, MPEP section 2113 states "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to the layers, collagen in combination with mineral components implicitly tends to separate into phases or layers. Note US 5,543,441, column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's position.

11. Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Constantz et al (5,279,831) in view of Liu (6,300,315) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view Sauk et al (4,780,450).

The teachings of Constantz, Liu, and Lussi, have been set forth above.

The references do not specify the instant collagen combination, i.e. type I and type III.

Sauk et al teach a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). Sauk teaches the collagen provides a structural matrix preventing migration of the calcium particles and the calcium phosphate particles also interact with the collagen to improve the physical properties of the collagen matrix by reducing its compressibility and increasing its mechanical strength. Sauk teaches not only does the combination provide a scaffold for new bone ingrowth but it mimics natural bone. A mixture of type I and type III collagen is taught (example 1). Sauk et al teach in column 2, line 60 to column 3, line 5, "the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of above references and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done in the implant art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27-28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,524,718 in view of in view of Liu (6,300,315) in view of Lussi et al (5,167,961).

Claim 1 is directed to a coated metallic implant comprising a metallic implant and an outer layer, wherein the outer layer comprises a bone analogous coating comprising a collagen matrix mineralized with a calcium phosphate phase which is adhered to said implant surface, wherein the mineralized collagen matrix is constructed in the form of layers and each layer comprises a network of mineralized collagen fibrils, amorphous calcium phosphate clusters, and crystalline hydroxyapatite.

US patent is directed to a metallic object and a thin polyphase oxide coating, where said polyphase oxide coating is comprised of a first phase, wherein said first phase is a metal oxide phase, and a second phase, wherein said second phase is either

an organic phase, an inorganic phase, or a combination of organic and inorganic phases, said polyphase oxide coating is produced by bringing the metallic substrate into contact with either an organic component, an inorganic component, or a combination of organic and inorganic components to be integrated into said polyphase oxide coating such that said second phase is present at or adjacent to the substrate surface and by simultaneously or subsequently anodically polarizing said substrate material in an electrolytic solution, wherein said metallic substrate is selected from the group consisting of aluminum, titanium, tantalum, zirconium, niobium, or their alloys, inclusive of intermetallic phases. Dependent claims are directed to the organic phases comprising collagen and the inorganic phases comprising calcium phosphate phases.

Liu teaches a mineralized collagen membrane for medical applications such as bone

substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such

as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at lest a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatite like crystallites with a particular degree of crystallinity, habit and size (irregular plate like morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodeled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4, lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone

mineral according to the invention may thus be used as a remodelling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20.

The difference between instant claims and US patent's claims is that the independent claim 1 requires specific calcium phosphates, i.e. hydroxyapatite and amorphous calcium phosphate. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the instantly claimed calcium phosphates and arrive at the instantly claimed invention. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly clamed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen. Further, Worch teaches the combination of calcium phosphate phase<u>s</u> and collagen wherein it is clear that Worch envisages utilizing more than one form of calcium phosphate in claim 4. Thus, the instantly claimed calcium phosphate types are considered an obvious modification. Note that the instant claims have comprising language and thus do not

exclude the oxide coating. Note the instant claims are rejected over the process claims of US patent since one would necessarily have the coated metallic implant of the instant invention by the process of making and a restriction was not made in US '718. With regard to the instantly claimed doping agents, it would have been obvious to dope Worch's mineralized collagen since Liu teaches the adding minor portions of fluoride or carbonate to the mineralized collagen to provide certain desired properties and to resemble or simulate biological apatite.

With regard to the instantly claimed drugs, it would have been obvious to add certain drugs depending on the desired effect of the implant as taught by Liu.

Further, the instant claims differ from US patent claims in that they recite a specific HA size. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Rhee et al and Lussi et al and utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster.

(10) Response to Argument

1. Claims 1, 4, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al

(5,279,831) optionally in further view of Lussi et al (5,167,961) as evidenced by US 5,543,441.

Appellants argue that there is a considerable difference between the structure of a simple mixture of collagen and calcium phosphate or hydroxyapatite, and the structure of a "mineralized collagen matrix". It is argued that the claimed metallic implant is coated with a mineralized collagen matrix that is structurally very different from a simple admixture of collagen and hydroxyapatite as disclosed or derivable from prior art. Appellants argue that the specification states: "The invention relates to a biomimetically produced bone analogous coating...". Based on the disclosure on page 3, lines 4-12 of the specification in reference to the prior art: "Methods which comprise both hydroxyapatite and collagen are only restricted to mixtures of the components .... ", it is argued that the specification clearly teaches a skilled worker that the mineralized collagen matrix according to the invention is not a simple mixture of hydroxyapatite and collagen, like the prior art, but is instead is biomimetically produced and bone analogous. Appellants refer to specification (and the claim language) that the matrix is biomimetically produced from an electrolyte solution. See page 4 line 39-40 of the specification. Appellants further argue that contrary to the examiner's assertion, the specification should also be relied for more than just lexicography or clear disavowal of claim scope to determine the meaning of a claim term when appellant acts as his or her lexicographer, the meaning of a particular term may be defined by implication. Appellants contend that the reference of Du et al supports their position, as seen from the description on page 519, col. 1, which states "Natural bone is a complex

biomineralized system with an intricate hierarchical structure. It is assembled through the orderly deposition of-apatite minerals within a type I collagenous organic matrix." Appellants state that Du describes HA crystals that grow in collage fibrils and in bone analogous structure that must be small enough to interact with collagen fibrils (0.3 microns to 3000 angstroms). It is argued that due to the applied electrochemical process the crystals cannot be larger than that. It is further argued that Du teaches a skilled worker that mineralized collagen is a common scientific term and it is not a simple mixture and that the mineralized bone analogous material can only be obtained under precise reaction conditions (such as soaking collagen in a phosphate solution of pH 14 followed by immersion in a calcium chloride solution). Further, appellants provide figures to demonstrate the difference between mineralized collagen according to the instant invention and a simple mixture of collagen and HA.

Appellants' arguments have been considered but not found persuasive because the specification does not define the term explicitly. Further, the specification does not state that mineralized collagen matrix excludes “simple mixtures of collagen and HA”. The examiners points to MPEP 2106 where it states, “Any special meaning assigned to a term must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention.” The appellants have not pointed to the page or pages in which the specification *explicitly* provides a definition of the term. Furthermore, the term “bone analogous coating” is also not defined. It is noted that the prior art of record also uses the term bone analogous. Therefore, the examiner is permitted the broadest reasonable

interpretation, which includes the definition of the term “Mineralize” by Merriam-Webster’s Collegiate Dictionary as: “to impregnate or supply with mineral”. Therefore, “mineralized collagen matrix” does not preclude a “simple” mixture of collagen and HA as argued by appellant. With respect to the argument regarding applicants is entitled to be his or her own lexicographer, MPEP 2106 states that inventor may define specific terms used to describe invention, but must do so “with reasonable clarity, deliberateness, and precision” and, if done, must “set out his uncommon definition in some manner within the patent disclosure’ so as to give one of ordinary skill in the art notice of the change” in meaning. It is further stated that “When a patentee acts as his own lexicographer in redefining the meaning of particular claim terms away from their ordinary meaning, he must clearly express that intent in the written description.” In this regard, appellants do not define the claimed term with reasonable clarity so as to distinguish from the simple mixtures of HA and collagen.

With respect to the argument regarding “biomimetically produced from an electrolyte solution”, product-by-process limitations, it appears appellant contends that a certain process of making the mineralized collagen matrix provides for a different structure than the prior art. The examiner directs applicant’s attention to MPEP 2113. “The Patent Office bears a lesser burden of proof in making out a case of prima facie obviousness for product-by-process claims because of their peculiar nature than when a product is claimed in the conventional fashion. In re Fessmann, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art,

although produced by a different process, the burden shifts to appellants to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983)". However, appellants have not demonstrated with evidence how the process limitations impart a structurally defining feature compared to the prior art of record. This is critical since appellants argue that "mineralized collagen matrix" is analogous to bone and JP '259 also teaches the coating is "close to osseous tissue". Thus, appellants must show that JP's plasma spraying process makes a materially different product. It should be noted that the attorney's arguments cannot take the place of evidence. See MPEP 716.01(c) (II). Examiner also notes while appellants state that Du teaches a specific method of forming bone analogous material, appellants also state that the membrane of Du cannot be used for the electrochemical process due lack of electrical charge on the membrane surface, which further supports examiner's contention that the terms "mineralized collagen" and "bone analogous coating" can be achieved in more than one ways. In this regard, appellants have not provided any comparative evidence that instant product is distinct from that of the prior art. With respect to the argument regarding comparative evidence based on FTIR data, while the data provided shows differences between collagen and HAP versus mineralized collagen, Constantz teaches HA prosthesis coating for natural bone in growth and the also teaches nucleation of the calcium phosphate crystals because of the intimate association caused by nucleation of the calcium phosphate within collagen. Constantz further recognizes the use of ions to modify the composition of HA, in order to influence

the dissolution behavior of coating. Appellants have not provided a comparison between instant product and that obtained by the combination of the teachings of JP, Constantz and Lussi.

Appellants argue that JP is silent regarding the particle size of HA or collagen, and also lacks a coated metallic implant with an outer layer of a bone analogous coating comprising collagen matrix in layers . It is argued that combining the teachings of JP and Constantz one would not arrive at the instant layered structure of mineralized collagen matrix and instead achieves a simple mixture of HA and collagen. Appellants also argue that Constantz teaches a coating comprising extremely small amounts of amorphous calcium phosphate and collagen but does not teach choosing the crystal size of 300 to 500 nm and that employing HA crystals in the 10 nm to 20,000 nm size range would form a simple mixture of HA with other materials. It is argued neither JP 259 nor Constantz teaches cathodic polarization and therefore the claimed crystal size within a layered mineralized collagen matrix would not be obvious. It is argued that Lussi does not teach hydroxyapatite crystals at all, much less crystals having a size of 300 to 500 nm. Appellants argue that while the natural and degreased bone material (of Lussi) may be used as a remodeling implant or prosthetic bone *replacement* and may be absorbed on physiologically active substances, Lussi et al. does not teach or suggest how and in which form the natural bone material can be absorbed on a substance. It is therefore argued that the combined teachings of JP 11-047259, Constantz et al. and Lussi et al. would lead a skilled worker to an implant coated with crystalline hydroxyapatite and optional collagen by simply dipping in a solution.

The arguments pertaining to “mineralized collagen matrix” have been discussed above. Moreover, the examiner notes that appellants have not specified the concentration of the amorphous phosphate and therefore, even “a small amount of amorphous phosphate” is enough to meet the claimed limitation. Regarding the particle size taught by Constantz, appellants’ argument is not persuasive because it is applicant’s burden to show the unobviousness of the instant narrow range, which is encompassed by the prior art. Note MPEP 2131.03. Moreover, if it is appellant’s position that the instant particle size is unexpected since it provides a bone analogous coating, the examiner points out that Lussi teaches this and thus it is not unexpected. With respect to the Appellants' argument that Lussi does not teach which form of natural bone is used, the examiner points out that Lussi teaches hydroxyapatite crystals. Note example 4. With respect to the argument that Lussi is not analogous art, the examiner directs appellants’ attention to column 4, lines 25-40 wherein Lussi discloses,

> The bone mineral according to the invention may thus be used as a remodelling implant **or prosthetic bone replacement**, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets.

Further JP ’’259 is directed to a prosthetic implant. Thus, both references are in the same field of endeavor.

Appellants argue that Rhee does not provide characteristics of these layers and is silent regarding the composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline HA. It is argued that Rhee teaches that the combination is instable and not ideal thus teaching away from the combination of collagen and

particulate minerals. Appellants' arguments have been considered but mot found persuasive because Rhee has been cited to show the inherent separation of collagen in combination with minerals and not for a stable combination of collagen with other minerals. Therefore for the same reason the argument that Rhee uses calcium phosphate crystals right from the start is not persuasive. Thus, it is the examiner's position that the instant inventions are rendered obvious.

2. Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view Sauk et al (4,780,450).

Appellants argue that like JP 259, Constantz and Lussi, Sauk also fails to teach electrochemical coating process and instead teaches porous composition. It is argued that Sauk et al. (US 4,780,450) relates to a porous composition comprising polycrystalline calcium phosphate ceramic, a phosphoryn calcium salt and type I collagen for application in osseous repair, which is obtained by a simple mixing of the components. It is argued that such a procedure would not give rise to a mineralized collagen matrix, with hydroxyapatite crystals formed directly on the collagen fibrils surface. Furthermore, Sauk et al. does not teach or suggest a mineralized collagen matrix comprising mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length between about 300 to 500 nm.

Appellants arguments are not persuasive because while the merits of JP ‘259, Constantz, and Lussi have been discussed above, Sauk has been cited for the specific types of collagen claimed i.e., type I and type II collagen. Sauk teaches that collagen provides a structural matrix preventing migration of the calcium particles and the calcium phosphate particles also interact with the collagen to improve the physical properties of the collagen matrix by reducing its compressibility and increasing its mechanical strength. Sauk teaches not only does the combination provide a scaffold for new bone ingrowth but it mimics natural bone. Since appellants have not provided any substantives arguments pertaining to this instant rejection, the rejection is maintained for the reasons of record.

3. Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Geistlich et al (5,573,771).

Appellants argue that Geistlich does not cure the shortcomings of JP, Constantz and Lussi. It is argued that the reference does not mention the applicability of bone material product for coating implants and similar to Lussi, Geistlich refers to a natural organic product. It is argued one skilled in the art confronted with the problem of manufacturing a synthetic implant coating for metallic implants would never have taken Geistlich into account as a relevant teaching. It is argued that Like Lussi, Geistlich is non-analogous art. Appellants arguments are not persuasive because while the merits

of JP ‘259, Constantz, and Lussi have been discussed above, the abstract of Geistlich clearly states “Such products are intended as remodeling implants or prosthetic bone replacement”, thus suggesting that Geistlich is in the same field of endeavor as that of JP, because JP also teaches prosthetic implant.

4. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Liu (6,300,315).

Appellants argue that Lui does not cure the deficiencies of JP ‘259, Constantz, and Lussi. Appellants argue that Lui does not teach the instant HA size. Appellant also argues that Lui teaches a process of precipitating calcium phosphate, which forms a loose network. Appellants’ arguments have been fully considered but they are not persuasive. The merits of JP ‘259, Constantz, and Lussi have been discussed above. The examiner points out that Lui is not relied upon to teach HA particle size since Constantz and Lussi cure this deficiency. The premise of the rejection is the obviousness of utilizing a mixture of different calcium phosphates, which appellant has not addressed. Appellants’ arguments pertaining to Lui’s process of making the coating is irrelevant since the instant claims are not directed to a process of making a mineralized collagen matrix. Therefore, it is the examiner’s position that the instant invention is rendered obvious.

5. Claims 1, 3-5, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441.

Appellant argues that the inorganic phase of Worch does not form multiple layers. Appellant argues that the claims have been amended to recite the coating is "adhered to the metallic implant which overcomes the rejection over Worch et al. Appellant argues that the coating of Worch are embedded in the oxide surface of the implant and not deposited on the implant surface. With respect to the term "embedded", appellant states that instant claims require "adhered to surface" and hence distinct from the "embedding" of Worch. It is argued that embedding refers to something that is an integral part and that the words into and onto do not mean the same. Appellant argues that Worch describes an electrochemical coating process which uses an anodic polarization process. Appellants' arguments have been fully considered but they are not persuasive. Appellants have not defined adhered and therefore the examiner is entitled to utilize the broadest *reasonable* interpretation. Secondly, the definition of adhered is to: To stick fast by or as if by suction or glue. To cause to adhere; make stick. Merriam Webster defines adhere as "to hold fast or stick by or as if by gluing suctions, grasping, or fusing." The examiner points out that term "adhered to" does not exclude embedding since embedding is a way of joining (sticking or fusing) two surfaces together. Worch discloses the phases are integrated by adsorption, sedimentation application, or

deposition. See column 2, line 65 to column 3, line 5. Thus, adsorption of Worch does include adhering on the surface. Worch also discloses that the inorganic and organic phases are integrated into the oxide phase and extend beyond it. See claim 23. Additionally, Worch discloses the metallic implant is inserted into a collagen solution so that the collagen fibrils adsorb to the surface of the implant. The examiner notes that the instant examples of the specification also immerse the implant into the collagen solution at the same pH and temperature. Appellants have not provided any persuasive arguments to overcome the rejection.

Regarding the product-by-process limitations, it appears appellants contend that a certain process of making the mineralized collagen matrix provides for a different structure than the prior art. The examiner directs appellant's attention to MPEP 2113. "The Patent Office bears a lesser burden of proof in making out a case of prima facie obviousness for product-by-process claims because of their peculiar nature than when a product is claimed in the conventional fashion. In re Fessmann, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to appellant to come forward with **evidence** establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983)". However, appellants have not demonstrated with evidence how the process limitations impart a structurally defining feature compared to the prior art of record. This is critical since appellants argue that the only difference in the process is that Worch

uses a anodic polarization process. It should be noted that the attorney's arguments cannot take the place of evidence. See MPEP 716.01(c) (II).

Therefore, it is the examiner's position that the Worch in view of Liu in further view of Lussi renders the instant invention obvious.

6. Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Sauk et al (4,780,450).

Appellants argue that the anodic process of Worch does not enable the precipitation formation of hydroxyapatite crystals on collagen fibrils. It is argued that Liu's process results in immediate precipitation of calcium phosphate, which does not promote the formation of calcium phosphate crystals directly on the collagen fibrils. It is argued that Lussi doe not teach HA crystals. It is argued that one cannot substitute native bone particles, which already exists in clusters and would not attach themselves to collagen fibrils. Appellants' arguments regarding Worch, Liu and Lussi have been addressed in the preceding paragraphs. Appellants have not argued the merits of the instant rejection which includes a further combination of Sauk. Therefore, it is the examiner's position that the instant claims are rendered obvious for the reasons of record.

7. Claims 1, 3-4, 8, 10, 12--16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441.

Appellants argue the particle sizes taught by Shirkanzadeh are too large to promote mineralization and thus do not resemble native bone. Appellants argue that an electrochemical precipitation process requires charged particles and Lui's particles do not possess any charges and therefore the combination would not provide the instant coating. Applicant argues that Lussi teaches away from the instant particle size.

Appellants' arguements have been fully considered but they are not persuasive. The examiner notes that Shirkanzadeh does not teach the instant particle sizes and thus the examiner relies on the Lussi. The merits of Lussi have been discussed above and are incorporated herein. With respect to the argument that Lussi does not teach the particle size of 20-400nm, the examiner points out that instant claims recite a range of about 300-500nm and not 20-400nm. Moreover, independent claim 26 does not recite any particle range.

The examiner notes that Shirkanzadeh is not limited to charged particles and appellants have not cited any specific column or line in which Shirkanzadeh requires only charged particles. Moreover, appellants have not cited any specific column or line in which Lui teaches away from an electric charge. Therefore, this argument is

unpersuasive since Shirkanzadeh applies a DC potential to charge particles. Therefore, the mineral used need not have a charge.

With regard to applellants' arguments that the prior art does not teach layers, the examiner cites US '441 to show that a combination of collagen and mineral is known to inherently separate into layers or phases. Therefore, it is the examiner's position that the instant invention is rendered obvious.

8. Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in view of Sauk et al (4,780,450).

Appellants argue that none of the references of record teach collagen matrix mineralized with calcium phosphate phase and collagen is type I to III. Appellants arguments are not persuasive because while the merits of Shirkanzadeh, Liu and Lussi have been discussed above, Sauk has been cited for the specific types of collagen claimed i.e., type I and type II collagen. Sauk teaches that collagen provides a structural matrix preventing migration of the calcium particles and the calcium phosphate particles also interact with the collagen to improve the physical properties of the collagen matrix by reducing its compressibility and increasing its mechanical strength. Sauk teaches not only does the combination provide a scaffold for new bone ingrowth but it mimics natural bone. Since appellants have not provided any substantives arguments pertaining to this instant rejection, the rejection is maintained for the reasons of record.

9. Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Geistlich et al (5,573,771).

It is argued that Shirkanzadeh does not teach the combination of amorphous calcium phosphate and hydroxyapatite or the instant particle size of HA and that the hydroxyapatite crystals of Shirkanzadeh are much too large for the purpose of forming a mineralized collagen matrix. It is argued that such large HA crystals would lead to a domination of the mineral component. It is argued that Liu is silent regarding a metal *surface* of a metallic implant and Liu's process results in immediate precipitation of calcium phosphate, which does not promote the formation of calcium phosphate crystals directly on the collagen fibrils. It is argued that Lussi et al., starts with native *degreased* bone particles and does not teach hydroxyapatite crystals at all much less crystals having a *size* of 300 to 500 nm. One cannot simply substitute native bone *particles,* which already exist as clusters and, as such, would not attach themselves to the collagen fibrils.

Appellants' arguements have been fully considered but they are not persuasive. The examiner notes that Shirkanzadeh does not teach the instant particle sizes and thus the examiner relies on the Lussi. The merits of Liu and Lussi have been discussed above and are incorporated herein. With respect to the argument that Lussi does not teach the particle size independent claim 26 does not recite any particle range.

The examiner notes that Shirkanzadeh is not limited to charged particles and appellants have not cited any specific column or line in which Shirkanzadeh requires only charged particles. Moreover, appellants have not cited any specific column or line in which Lui teaches away from an electric charge. Therefore, this argument is unpersuasive since Shirkanzadeh applies a DC potential to charge particles. Therefore, the mineral used need not have a charge.

With regard to applellants' arguments that the prior art does not teach layers, the examiner cites US '441 to show that a combination of collagen and mineral is known to inherently separate into layers or phases. Therefore, it is the examiner's position that the instant invention is rendered obvious.

10. Claims 1, 3-6, 8, 10, 12-16, 18-19, 23-25, 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Constantz et al (5,279,831) in view of Liu (6,300,315) optionally in further view of Lussi et al (5,167,961) and as evidenced by US 5,543,441.

Appellants argue that there is not teaching in Constantz to use cathodic polarization in coating process and the process of Constantz only teaches a simple mixture of HA and collagen and not mineralized collagen. It is argued that Constantz does not suggest 300 to 500 nm crystal size and therefore a skilled worker using HA crystals in 10-20000 nm range would form a simple mixture. It is argued that Liu is silent regarding the metal surface of a metallic implant and Lussi uses purified native

bone particles, thus teaching away from selecting the particle of HA of the instant invention. It is argued that Rhee teaches away from a layered implant.

Appellants' arguments have been considered but not found persuasive because Constantz teaches HA prosthesis coating for natural bone in growth and the also teaches nucleation of the calcium phosphate crystals because of the intimate association caused by nucleation of the calcium phosphate within collagen. Constantz further recognizes the use of ions to modify the composition of HA, in order to influence the dissolution behavior of coating. Appellants have not provided a comparison between instant product and that obtained by the combination of the teachings of Constantz, Liu and Lussi. The arguments pertaining to “mineralized collagen matrix” have been discussed above. Moreover, the examiner notes that appellants have not specified the concentration of the amorphous phosphate and therefore, even “a small amount of amorphous phosphate” is enough to meet the claimed limitation. Regarding the particle size taught by Constantz, appellants’ argument is not persuasive because it is applicant’s burden to show the unobviousness of the instant narrow range, which is encompassed by the prior art. Note MPEP 2131.03. Moreover, if it is appellant’s position that the instant particle size is unexpected since it provides a bone analogous coating, the examiner points out that Lussi teaches this and thus it is not unexpected. With respect to the Appellants' argument that Lussi does not teach which form of natural bone is used, the examiner points out that Lussi teaches hydroxyapatite crystals. Note example 4. With respect to the argument that Lussi is not analogous art, the examiner directs appellants’ attention to column 4, lines 25-40 wherein Lussi discloses,

> The bone mineral according to the invention may thus be used as a remodelling implant **or prosthetic bone replacement**, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets.

Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Therefore, a skilled artisan would have been motivated to utilize the calcium phosphates with collagen since Liu demonstrates the state of the art wherein it is known to add claimed calcium phosphates with collagen for mineralization.

Appellants argue that Rhee does not provide characteristics of these layers and is silent regarding the composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline HA. It is argued that Rhee teaches that the combination is instable and not ideal thus teaching away from the combination of collagen and particulate minerals. Appellants' arguments have been considered but mot found persuasive because Rhee has been cited to show the inherent separation of collagen in combination with minerals and not for a stable combination of collagen with other minerals. Therefore for the same reason the argument that Rhee uses calcium phosphate crystals right from the start is not persuasive. Thus, it is the examiner's position that the instant inventions are rendered obvious.

11. Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Constantz et al (5,279,831) in view of Liu (6,300,315)

optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view Sauk et al (4,780,450).

Appellants' arguments regarding the teachings of Constantz, Liu and Lussi have been addressed in the previous paragraph. It is argued that Sauk does not give rise to mineralized collagen matrix. It is argued that Sauk fails to teach the electrochemical process for coating implant and instead teaches a porous composition comprising polycrystalline calcium phosphate ceramic, a phosphoryn calcium salt and type I collagen for application in osseous repair, which is obtained by a simple mixing of the components. It is argued that such a procedure would not give rise to a mineralized collagen matrix, with hydroxyapatite crystals formed directly on the collagen fibrils surface. Furthermore, it is argued that Sauk et al. does not teach or suggest a mineralized collagen matrix comprising mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length between about 300 to 500 nm.

Appellants arguments are not persuasive because Sauk has been cited for the specific types of collagen claimed i.e., type I and type II collagen. Sauk teaches that collagen provides a structural matrix preventing migration of the calcium particles and the calcium phosphate particles also interact with the collagen to improve the physical properties of the collagen matrix by reducing its compressibility and increasing its mechanical strength. Sauk teaches that not only does the combination provide a scaffold for new bone ingrowth but it mimics natural bone. Since appellants have not provided any substantives arguments pertaining to this instant rejection, the rejection is maintained for the reasons of record.

12. Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27-28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,524,718 in view of in view of Liu (6,300,315) in view of Lussi et al (5,167,961).

Appellants argue that the claims of Worch do not teach multiple layers on the implant surface. It is argued that the anodic process of Worch's claims do not enable the precipitation and formation of hydroxyapatite crystals on the collagen fibrils. Appellants argue that an electrochemical precipitation combined with the formation of seed crystals on the fibrils as well as the implant coating occurs only in a cathodic polarization process. It is stated that in the course of the cathodically conducted coating process calcium phosphate crystals with a length of about 300 to 500 nm are formed and precipitated onto the collagen fibrils forming mineralized collagen fibrils that precipitate onto the implant surface.

Regarding the product-by-process limitations, it appears appellants contend that a certain process of making the mineralized collagen matrix provides for a different structure than the prior art. The examiner directs appellant's attention to MPEP 2113. "The Patent Office bears a lesser burden of proof in making out a case of prima facie obviousness for product-by-process claims because of their peculiar nature than when a product is claimed in the conventional fashion. In re Fessmann, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to appellant to come forward

with **evidence** establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983)". However, appellants have not demonstrated with evidence how the process limitations impart a structurally defining feature compared to the prior art of record. This is critical since appellants argue that the only difference in the process is that Worch uses an anodic polarization process. It should be noted that the attorney's arguments cannot take the place of evidence. See MPEP 716.01(c) (II).

Appellants argue that Liu et al. does not cure the deficiencies of Worch since Liu do not claim hydroxyapatite crystals having a length of about 300 to 500 nm. It is argued that Lussi process starts with natural ground bone and the claims of Lussi does not teach or suggest hydroxyapatite crystals at all and they are particularly silent regards HA crystals having a size of 300 to 500 nm. Therefore, it is argued that the claims of Worch, Liu and Lussi do not teach or suggest a mineralized collagen matrix that is constructed in the form of layers, whereby at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite, wherein the crystals of said crystalline hydroxyapatite have a length of about 300 to 500 nm. It is argued that they are particularly silent regarding a metallic implant coated with a mineralized collagen matrix that is prepared by a cathodic process and therefore, the above remarks is respectfully requested that the obviousness- type double patenting rejection be reversed.

Appellants arguments have been considered but not found persuasive because firstly, the premise of the double patenting rejection made in view of secondary

references is not limited to the claims of Liu and Lussi (secondary references) and instead the entire disclosure. The rejection is based on the claims of Worch in view of the entire disclosures of Liu or Lussi. Further, with respect to the Appellants' argument that Lussi does not teach which form of natural bone is used, the examiner points out that Lussi teaches hydroxyapatite crystals. Note example 4. With respect to the argument that Lussi is not analogous art, the examiner directs appellants' attention to column 4, lines 25-40 wherein Lussi discloses,

> The bone mineral according to the invention may thus be used as a remodeling implant **or prosthetic bone replacement**, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodeling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets.

With respect to Liu, the reference has been cited for a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Liu has not been cited for the claimed crystal sizes. With respect to the layers of instant claims, it is evident from the teachings of Rhee that a combination of collagen and mineral is known to inherently separate into layers or phases.

Therefore, it is the examiner's position that the Worch in view of Liu in further view of Lussi renders the instant invention obvious.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Lakshmi S Channavajjala/

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/MP WOODWARD/

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